REMARKS

The status of the claims is as follows:

Original:	16-19
Currently amended:	11
Previously presented:	1-3, 9, 20 and 21
Canceled:	4-8, 10, 12-15
New:	None

With entry of this amendment, claims 1-3, 9, 11 and 16-21 are pending. Reconsideration is requested.

Claim 10 is canceled herein. Claims 4-8 and 12-15 were canceled in previous amendments.

Claim 11 has been amended to remove recitation directed to preventing.

None of the amendments introduces new matter.

This amendment is being made without prejudice. Applicants reserve the right to pursue any or all of the subject matter recited in the canceled claims and any or all subject matter removed from the pending claims in one or more continuing applications.

Correction of Inventorship under 37 CFR § 1.48

A request for correction of inventorship under Rule 1.48 was filed on August 21, 2008. It is requested that the status of this request be reported in the next communication to Applicants.

Information Disclosure Statement

An information disclosure statement (IDS) accompanies this amendment. The IDS includes: (i) an update on the interference declared between U.S. serial no. 10/587,601 and US 7,211,572 (Miyazaki); (ii) granted US patents or published US patent applications corresponding to several of the published international applications cited in the IDS filed July 28, 2006; (iii) a granted US patent corresponding to a published US application cited in the IDS filed July 28, 2006; and (iv) several new references. Copies of all the references are enclosed with the IDS except for US patents and US published applications.

Allowable Subject Matter

The Examiner's conclusion that claims 1-3, 9 and 16-21 are in condition for allowance is acknowledged.

Rejection under 35 U.S.C. § 112

Claims 10 and 11 have been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification. Claim 10 has been canceled rendering the rejection moot as applied thereto. Claim 11 has been amended to remove the recitation directed to preventing. The rejection is traversed with respect to claim 11 as amended herein.

It is noted that: (1) all documents referenced in the remarks below are cited in the accompanying IDS and copies thereof are enclosed with the IDS, except for Remington's Pharmaceutical Sciences; and (2) the text in the specification referred to in the remarks below is fully supported by U.S. provisional application no. 60/551,625, filed March 9, 2004, to which a benefit of priority has been claimed.

Claim 11 as amended is directed to a method of treating HIV infection, treating AIDS, or delaying the onset of AIDS. The specification provides sufficient disclosure to enable a person of ordinary skill in the art to make and use the invention as set forth in claim 11 without undue experimentation. More particularly, the specification discloses that HIV is the etiological agent responsible for AIDS (page 1, lines 16-19), that integration of the proviral DNA into the host cell genome is a required step in HIV replication (page 1, lines 20-22), and that HIV integrase, the enzyme mediating the integration of the proviral DNA, is one of the enzymes that has been shown to be essential for the replication of HIV (page 1, line 31). The person of ordinary skill in the art would also have had knowledge of LaFemina et al., *J. Virology* 1992, 66(12), pp. 7414-7419, which provides evidence that the integrase enzyme is required for the productive infection of human T-lymphoid cells.

The specification further discloses that the hydroxy polyhydro-2,6-naphthyridine dione compounds of the present invention are useful in the inhibition of HIV integrase, the treatment of infection by HIV, the treatment of AIDS and the delay in the onset of AIDS (page 2, lines 26-31; page 45, lines 19-25). The specification provides comprehensive guidance and directions on how to prepare the compounds of the invention (note: Schemes 1 to 5 and the detailed experimentals in Examples 1, 2, 8, 9, 10-1, 11 and 16 are disclosed in the first priority application). The specification further discloses that compounds representative of the compounds of the present invention have been shown by testing in suitable assays to inhibit HIV integrase (Example 89) and to inhibit the replication of HIV (Example 90).

The specification also discloses means for administering the claimed compounds (page 47, lines 6-17), provides guidance on the preparation of pharmaceutical compositions for administration of the compounds including a cite to the 18th edition of Remington's Pharmaceutical Sciences (page 47, lines 17-28), and provides guidance on suitable dosage ranges for oral administration of the compounds (page 47, line 29 to page 48, line 9).

Applicants' position is that this disclosure is sufficient to enable claim 11 as amended. More particularly, using this description, optionally in combination with know-how available in the art, the person of ordinary skill can without undue experimentation prepare and administer a compound of the invention in a suitable carrier and in the appropriate dosage form and dosage amount to a subject in order to treat HIV infection, treat AIDS, or delay the onset of AIDS.

In the Office Action, the Examiner notes (page 4, lines 5-6) that the pharmaceutical art is unpredictable and asserts that no examples of test compounds to treat HIV or delay AIDS has been provided. The Examiner is referred to Examples 89 and 90 wherein it is disclosed that representative compounds of the invention exhibit inhibition of strand transfer activity in HIV integrase and inhibition of HIV replication. Representative compounds of the invention include the compounds set forth in the examples and all of the examples (excepting Examples 16 and 17

which it is believed were not tested) were determined to have IC_{50} values less than about 1 μM in the strand transfer assay and IC_{95} values less than about 10 μM in the replication inhibition assay. (Note: Not all of the compounds in the examples are embraced by main compound claim 20, from which claim 11 depends, but a clear majority of them do fall within claim 20 including all of the compounds – i.e., Examples 1-9, 10-1, 11 and 16 -- specifically disclosed in the first priority application.)

The compounds of Examples 1-87 are all hydroxy polyhydro-2,6-naphthyridine diones having an assortment of substituents. All of the compounds embraced by the instant claims possess the same hydroxy polyhydro-2,6-naphthyridine dione core present in the exemplified compounds. The person of ordinary skill in the art would understand that this core structure represents a substantial technical feature present in all of the exemplified compounds and would believe that the core structure is the basis for the integrase inhibition activity and HIV replication inhibition activity of these compounds. The skilled artisan would further expect that the activity exhibited by the compounds in the examples would be seen in other compounds embraced by claim 11, all of which have the core structure. The activity of the compounds within the scope of the claim would vary with the type and number of substituents attached to the core, but the skilled artisan would expect that other compounds falling within the scope of claim 11 to share the same physiological activity as the exemplified compounds.

The Examiner has also asserted (page 4, lines 14-16) that there is no guidance for using a claimed compound to treat any and all HIV disease. Applicants disagree. Given the discussion above, the person of ordinary skill in the art would understand that the claimed compounds are HIV integrase inhibitors that will inhibit HIV integrase and HIV replication upon contact with the virus. The person of ordinary skill in the art would also understand that, because the claimed compounds will inhibit HIV replication, there is a reasonable expectation that they will be effective in the treatment of HIV infection.

The skilled artisan would also reasonably expect the compounds to be effective in delaying the onset of AIDS and in treating AIDS. It was known prior to the filing of the instant application that infection by HIV can result in the progressive destruction of the immune system, specifically the depletion of CD4-positive T lymphocytes, resulting in acquired immune deficiency syndrome (AIDS) (Fauci et al., Ann. Int. Med., 100, 92-106 (1984); see also page 1, lines 18-21 of the subject application). It was also known that increases in HIV viral load are correlated to AIDS progression, and thus limiting the spread of the HIV virus will limit the viral load and postpone the onset of AIDS (Dean et al., Science, 273, 1856-62 (1996)). In other words, AIDS and the diseases and conditions associated with AIDS are due directly or indirectly to a compromised immune system which is the result of significant and/or prolonged HIV infection. Administration of appropriate HIV antiviral agents such as the claimed compounds can reduce the viral load to such a level that the onset of AIDS can be delayed or the progression of AIDS ameliorated or even reversed.

It is further noted that there is nothing unusual or difficult in the practice of the methods recited in claim 11; i.e., the compounds are administered to an individual in need of treatment of HIV infection, treatment of AIDS, or delay in the onset of AIDS. Identification of individuals infected by HIV and thus in need of treatment was well known in the art before the filing date of

this application; i.e., numerous tests were available for diagnosis of HIV infection. See, for example, Mylonakis et al., *Am. J. Med.* November 2000, 109, pp. 568-576; *Med. Lett. on Drugs & Therapeutics* 1997, 39 (1008), pp. 81-83; and Constantine, *AIDS* 1993, 7, pp. 1-13. Furthermore, plasma viral load and CD4+ lymphocyte count were well established as prognostic markers for HIV. See, for example, Mellors et al., *Annals of Internal Medicine* 1997, 126 (12), pp. 946-954. Treatment of HIV infection or AIDS, and delay in the onset of AIDS are produced in the patient by bringing the HIV-infected cells into contact with an effective amount of the claimed compound. Modes of administration for achieving such contact and dose ranges suitable for administration are described in the specification. The person of ordinary skill in the art can apply this disclosure in combination with his general knowledge of the pharmaceutical art to administer the claimed compound in an amount effective for the treatment of HIV infection or AIDS, or for a delay in the onset of AIDS.

In view of the foregoing remarks and the amendments to the claims, withdrawal of the section 112 rejection of claim 11 is requested.

The application is believed to be in condition for allowance and passage to issue is requested. The Examiner is invited to telephone the undersigned should any minor matters need to be resolved before a Notice of Allowance can be mailed.

Respectfully submitted,

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